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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/035,832	12/26/2001	David W. Morris	CHIR0021-100 (PP23698.001	1729

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EXAMINER	
HOLLERAN, ANNE L	

ART UNIT	PAPER NUMBER
1643	

DATE MAILED: 12/15/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/035,832	MORRIS ET AL.	
	Examiner	Art Unit	
	Anne L. Holleran	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 September 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *20-35* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *20-35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group 7057 (with species election of SEQ ID NO: 1587) in the reply filed on 9/21/2006 is acknowledged. The traversal is on the ground(s) that it would not pose a serious burden on the examiner to examine Group 7057 along with groups 2353-3538 to the extent these groups read on detecting expression of SEQ ID NO: 1587. This is not found persuasive because as discussed in the previous Office action, the methods of group 7057 and those of 2353-3528 comprise different steps and have different outcomes, because the methods of group 7057 are directed to detecting differential expression for the purpose of diagnosing cancer, whereas the methods of 2353-3528 comprise detecting expression after a candidate agent has been added to cells for the purpose of screening for agents that have anti-cancer activity. The search and examination of each of these groups involves more than a database search of the recited sequences, because the purposes of the methods and the steps of the methods must be searched and examined as well. The requirement is still deemed proper and is therefore made FINAL.

2. The preliminary amendment is acknowledged. Claims 1-19 were cancelled. Claims 20-38 were added. Claims 36-38, drawn to non-elected inventions, are withdrawn from consideration. Claims 20-25 are examined on the merits.

Claim Rejections - 35 USC § 112

3. Claim 35 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 35 is indefinite because of the phrase "complement thereof". Because the term "complement" includes polynucleotides that are not completely complementary to the reference sequence, where the "complement" is complementary at either end of the sequence but not in the middle of the sequence, the scope of the claimed polynucleotides is indefinite. Applicant is advised to amend the claims to recite "fully complementary".

4. Claims 21 and 24 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The basis of this rejection is that the amendment introducing claims 21 and 24 adds new matter to the specification as originally filed, because there is no support in the specification for the use of measurement of differential expression of PPP3CC for the purpose of detecting a propensity towards cancer.

Claims 21 and 24 are dawn to methods comprising the detection of expression of PPP3C, wherein differential expression of PPP3CC or up-regulation of expression of PPP3CC is evidence that a patient has a propensity towards cancer. The amendment points to support for the newly added claims. However, the passages pointed to and the originally filed claims

provide support for the concept of diagnosing cancer by measuring differential expression of cancer associated sequences such as PPP3CC, but fails to provide support for the concept of a method performed for the purpose of assessing a patient's risk of developing cancer. The general discussion in the specification of what is meant by the term "diagnosis" does not appear to include the concept of risk assessment, nor is there any discussion in the specification of the concept that the PPP3CC expression is associated with the development of cancer. Therefore, claims 21 and 24 introduce new matter into the specification as originally filed.

5. Claims 20-35 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of diagnosis of colon cancer comprising the differential detection of PPP3CC protein levels, does not reasonably provide enablement for methods for diagnosing any and all cancers or for the detection of a propensity towards cancer, comprising either the differential detection of PPP3CC protein or the differential detection of PPP3CC mRNA levels. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. The basis for this rejection is that the teachings of the specification do not enable the intended use of the claimed methods for the diagnosis of any and all cancers.

Factors to be considered in determining whether undue experimentation would be required to practice the full scope of the claimed inventions are: 1) quantity of experimentation necessary; 2) the amount of direction or guidance presented in the specification; 3) the presence or absence of working examples; 4) the nature of the invention; 5) the state of the prior art; 6) the

relative skill of those in the art; 7) the predictability or unpredictability of the art; and 8) the breadth of the claims. See In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988).

The specification provides the nucleotide genomic, mRNA and coding sequences of a gene referred to as human PPP3CC. A search of SEQ ID NO: 1587, which corresponds to the human PPP3CC mRNA sequence (se Table 108, page 204 of preliminary amendment filed 7/22/2002), provides a match with a sequence that encodes human calcineurin A (see Muramatsu, T. et al. Biochemical and Biophysical Research Communications, 188: 265-271, 1992), a calmodulin-dependent protein phosphatase. Calcineurin A is also known as PP2B. The specification provides no other teachings that are specific to the sequence of SEQ ID NO: 1587 (or the genomic or the coding sequences). The support for methods of diagnosis amounts to a supposition that detection of PPP3CC protein or encoding nucleic acids correlates with any and all cancer, or with the specific cancers of lymphatic tissue, prostate tissue, stomach tissue and breast tissue, because the specification lacks working examples demonstrating a correlation between levels of PPP3CC and cancer.

The art of cancer diagnosis is unpredictable and requires the establishment of certain criteria before the measurement of a marker can be considered a marker for early detection of cancer. For example, Tockman (Tockman, M.S. et al. Cancer Research, (Suppl.) 57: 2711s-2718s, 1992) teaches that the application of a marker for diagnostic purposes requires a provision of a clear definition of the end point for which the candidate protein or gene is to be a marker; an identification of the relevant clinical specimen in which to detect the marker, and the establishment of a range of marker variability (page 2711s, 2nd column). Furthermore, with respect to PPP3CC (calcineurin or PP2B), the data in the prior art and also post-filing date art

does not indicate that any of the benchmarks cited by Tockman have been achieved.

Lakshmikuttyamma (Lakshmikuttyamma, A. et al., Journal of Cellular Biochemistry 95: 731-739, 2005) demonstrates that increased levels and increased activity of calcineurin is found in deeply invading colon cancer cells, and that a moderate amount relative to non-cancerous tissues is found in colon polyps. Therefore, Lakshmikuttyamma concludes that calcineurin acitivity and amounts are related to development of colon carcinoma. However, Lakshmikuttyamma fails to establish a range of marker variability and does not establish that calcineurin levels may be used to diagnose a propensity to colon cancer. Furthermore, even if it is reasonable to extrapolate from the data in Lakshmikuttyamma to a method for the diagnosis of colon cancer based on observing an increase in calcineurin activity of protein levels, one cannot extrapolate the data of in Lakshmikuttyamma to a method where the diagnosis is based on observations of mRNA levels. Even further, it would not be reasonable to extrapolate the data of in Lakshmikuttyamma to a method for the diagnosis of any and all cancers.

The only other system that has been investigated with respect to calcineurin protein levels or enzyme activity is in the cells of the immune system. In this system what has been found is that inhibition of calcineurin activity may be associated with different types of leukemia. For example, Kihara teaches that inhibition of calcineurin activity appears to lead to augmentation of proliferation in HL-60 cells (Kihara, H. et al, International Journal Oncology 12: 629-634, 1998). Padma (Padma, S. et al, Clinica Chimica Acta, 321: 17-21, 2002) suggests that assay of calcineurin activity may be of use in diagnosis and prognosis of leukemia and found decreased activity but not content of PP2B was associated with leukemia. Taken together it appears that while an increase in protein levels and enzyme activity is associated with colon cancer, the

opposite is true for cells of the immune system. Therefore, the observation of differential expression of calcineurin in one type of cancer does not appear to make it predictable that levels of calcineurin may be useful for the diagnosis of cancer in general or of a second cancer. With respect to cancers of the immune system, changes in levels of calcineurin do not appear to be diagnostic for cancer, instead possibly changes in enzyme activity of calcineurin may be the marker that might be established at some future date.

Therefore, further research would be required for one of skill in the art to practice the full scope of the invention for the purpose of using the claimed methods for the diagnosis of cancer or for determining if an individual has a propensity to develop cancer, because neither the specification nor the prior art has established that calcineurin protein or mRNA levels are associated with a cancer phenotype. The post-filing date art appears to provide an indication that observations of increased calcineurin protein levels may be useful in the detection of colon cancer, but not as a marker of a propensity to develop colon cancer, because there is no data demonstrating that healthy individuals may be screened on the basis of certain levels of either calcineurin protein or mRNA. The further research that would be required to practice the full scope of the claimed invention would be undue experimentation because it would require first establishing whether changes in calcineurin protein or mRNA levels is in fact associated with a specific type of cancer, which is research directed to an unpredictable conclusion. This is differentiated from the situation in Wands where the further research was in the realm of routine experimentation to screen for hybridomas that bound to a specific antigen, where the likelihood was extremely high that a monoclonal antibody could be made once one of skill in the art was in possession of a given antigen.

6. Claims 20-27 and 29-35 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods where the expression product that is detected is an mRNA having a sequence of SEQ ID NO: 1587, does not reasonably provide enablement for methods where the expression product that is detected is an mRNA having a sequence at least 98% identical to SEQ ID NO: 1587, 95% identical to SEQ ID NO: 1587, or is greater than about 75% in overall homology to SEQ ID NO: 1587. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Even if the prior rejection under 112, 1st paragraph is overcome, the following rejection will be applied. The broadest claim is drawn to a method for diagnosing cancer comprising detecting evidence of differential expression of PPP3CC in a patient sample, wherein evidence of differential expression indicates that the patient has cancer. The specification, at page 12, line 26 teaches that a nucleic acid is a "CA nucleic acid" if the overall homology of the nucleic acid sequence to one of the nucleic acid of Tables 1-112. PPP3CC is defined in Table 108 as having a human genomic sequence of SEQ ID NO: 1586, human mRNA sequence of SEQ ID NO: 1587 and SEQ ID NO: 1588. Therefore, the broadest claim may be interpreted as a method for diagnosis of cancer comprising detecting evidence of differential expression of a sequence having greater than about 75% overall homology to SEQ ID NO: 1587.

Factors to be considered in determining whether undue experimentation would be required to practice the full scope of the claimed inventions are: 1) quantity of experimentation necessary; 2) the amount of direction or guidance presented in the specification; 3) the presence or absence of working examples; 4) the nature of the invention; 5) the state of the prior art; 6) the

relative skill of those in the art; 7) the predictability or unpredictability of the art; and 8) the breadth of the claims. See In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988).

The specification provides no working examples to demonstrate an association between expression of PPP3CC in any form and any type of cancer. Post-filing date art appears to indicate that levels of the protein product of PPP3CC coding sequence may be useful in the detection of colon carcinoma (discussed above), but there is no indication that variants or mutants or mRNA levels may be useful. Because of the broadly recited claims, the methods read on the detection of mutations of calcineurin and the detection of mutations for the detection of cancer or for the assessment of risk associated with developing cancer. The specification provides no working examples indicating that mutations of calcineurin are known, or that any type of mutation is known to be associated with any type of cancer. Therefore, the specification appears to present nothing more than invitation to research to find out whether mutations exist which may be correlated with a cancer phenotype. This situation appears to be analogous to the situation in Brenner v. Manson (148 USPQ 689 (1966) in which the patent protection was sought for compounds having structures that were similar to a compound with a known utility. The courts concluded that "a patent is not a hunting license...[i]t is not a reward for the search, but compensation for its successful conclusion." In the instant case, even if applicant's establish that detection of mRNA having the sequence of SEQ ID NO: 1587 is useful for the diagnosis of cancer, this will not enable the claimed methods because the claimed methods include those that comprising the detection of mRNA having a sequence that is greater than 75% in overall homology to SEQ ID NO: 1587, and the specification has not provided any data or line of

reasoning to demonstrate that sequences having this variability in nucleic acid homology to SEQ ID NO: 1587 are associated with any type of cancer.

7. Claims 20-27 and 29-35 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The basis for this rejection is that the specification fails to describe the genus of mRNA expression products of PPP3CC that have greater than 75% sequence identity to SEQ ID NO: 1587 and that are also diagnostic of cancer or diagnostic for a specific cancer. Therefore, the specification lacks adequate written description for the broadly claimed methods.

As discussed above in section #6, the specification fails to provide an enabling disclosure for the broadly claimed methods of diagnosing cancer by the detection of differential expression of PPP3CC, where this is broadly interpreted as reading on methods where differential detection of mRNA having a sequence that is greater than 75% in sequence homology with SEQ ID NO: 1587. The specification fails to provide adequate written description of the genus of PPP3CC expression products that are diagnostic of cancer.

For a claim drawn to a genus, the written description requirement may be satisfied through sufficient description of a representative number of species by actual reduction to practice or by disclosure of relevant, identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying

characteristics, sufficient to show the applicant was in possession of the claimed genus. A "representative number of species" means that the species, which are adequately described, are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus (see Official Gazette 1241 OG 174, January 30, 2001). In the instant case, there is substantial variation in the genus for the broad claims because expression products of PPP3CC may be interpreted as having greater than 75% sequence identity to SEQ ID NO: 1587. For the narrower claims that recite 98% or 95% sequence identity, the specification also fails to provide support because there is not even one representative species of diagnostic mRNA product that has been shown to be diagnostic of any type of cancer. Therefore, applicant does not appear to be in possession of the broadly claimed methods.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

8. Claims 20-24 are rejected under 35 U.S.C. 102(e) as being anticipated by Venter (US 6,812,339; issued Nov. 2, 2004; effective filing date Oct. 20, 2000).

Claims 20-24 are drawn to methods comprising the step of detecting evidence of differential expression of PPP3CC in a patient sample. The intended use of the claimed methods is for the diagnosis of cancer, wherein evidence of differential expression indicates that the patient has cancer, or has a propensity towards cancer, wherein the cancer is selected from the group consisting of carcinoma, lymphoma, leukemia, prostate cancer, stomach cancer and breast cancer, wherein PPP3CC gene expression in the patient sample is up-regulated relative to PPP3CC gene expression in normal tissue, wherein the up-regulation of expression indicates that the patient has a propensity towards cancer. Because the claims comprise the one active step of detecting evidence of differential expression of PPP3CC in a patient sample, the claims broadly read on any methods that comprise the same step of detecting differential expression, even if prior art methods do not explicitly recognize that the detection step could be used for the diagnosis of cancer. It is noted that the specification teaches at page 6, line 26 that differential expression includes within its scope that a gene is differentially expressed, activated, inactivated, altered, up-regulated, or down-regulated etc..... Therefore, detection of any type of difference in PPP3CC gene expression is within the scope of the claims.

Venter teaches biological assays (see column 14, lines 39-47) for SNPs of SEQ ID NOS: 1-5871 (transcript sequences). Venter's SEQ ID NO: 771 is the same as applicants' SEQ ID NO: 1587, which is a human PPP3CC mRNA sequence (see Table 108 of instant specification). Venter teaches a hybridization assay where a probe hybridizes to a segment of target DNA from one individual but does not hybridized to a corresponding segment from another individual due presence of different polymorphic forms in the respective segments from the two individuals (see

column 15, lines 12-17). Therefore, Venter teaches a method that is the same as that claimed, because Venter's method comprises the same active step as recited in claims 20-24.

9. Claims 20-26, 29, 30, and 34 are rejected under 35 U.S.C. 102(b) as being anticipated by Yamamoto (Yamamoto, M. et al. Leukemia, 13: 595-600, 1999).

Yamamoto teaches a method of measuring the level of PP2B protein (calcineurin; a protein that is encoded by SEQ ID NO: 1587, which encodes PPP3CC) in leukemic cells from patients with acute myelogenous leukemia (AML), common acute lymphocytic leukemia (cALL), and chronic lymphocytic leukemia (CLL), and in normal peripheral leukocytes (page 596, 1st to 2nd column, bridging paragraph; and 2nd column). The leukemic cells were from 85 adult Japanese patients. The normal peripheral blood leukocytes were from 10 normal healthy donors (page 595, see abstract, and 2nd column). Yamamoto compared the levels of PP2B protein in normal cells to PP2B protein in leukemic cells (see Figure 2, page 597). Therefore, Yamamoto teaches a method that is the same as that claimed.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne Holleran, whose telephone number is (571) 272-0833. The examiner can normally be reached on Monday through Friday from 9:30 am to 5:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, can be reached on (571) 272-0832. Any inquiry of a general nature or relating to the

status of this application or proceeding should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The Official Fax number for Group 1600 is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

Anne L. Holleran
Patent Examiner
December 8, 2006

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SUPERVISORY PATENT EXAMINER